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# Remington's

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*Editor, and Chairman  
of the Editorial Board*

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Table II—Nominal Dimensions of Standard Sieves

No.	Sieve opening		Permissible variation in average opening, %	Permissible variation in maximum opening, %	Wire diameter, mm
	mm	$\mu\text{m}$			
2	9.52	9520	$\pm 3$	+ 5	2.11 to 2.59
4	4.76	4760	$\pm 3$	+10	1.14 to 1.68
8	2.38	2380	$\pm 3$	+10	0.74 to 1.10
10	2.00	2000	$\pm 3$	+10	0.68 to 1.00
20	0.84	840	$\pm 5$	+15	0.38 to 0.55
30	0.59	590	$\pm 5$	+15	0.29 to 0.42
40	0.42	420	$\pm 5$	+25	0.23 to 0.33
50	0.297	297	$\pm 5$	+25	0.170 to 0.253
60	0.250	250	$\pm 5$	+25	0.149 to 0.220
70	0.210	210	$\pm 5$	+25	0.130 to 0.187
80	0.177	177	$\pm 6$	+40	0.114 to 0.154
100	0.149	149	$\pm 6$	+40	0.096 to 0.125
120	0.125	125	$\pm 6$	+40	0.079 to 0.103
200	0.074	74	$\pm 7$	+60	0.045 to 0.061

particles in a liquid of a relatively low density, under the influence of a gravitational or centrifugal field. In free settling (i.e., no particle-particle interference) the particles are supported by hydraulic forces and their fall can be described by Stokes' law. However, in most real situations particle-particle interference, nonuniformity, and turbulence are all present, resulting in more complex settling patterns. The Andreason pipet, which is based on sampling near the bottom of a glass sedimentation chamber, is perhaps the best known of the early instruments. With centrifugation, entrainment of particles in the currents produced by other particles may also interfere with fractionation.

Gravitational settling chambers are often used for large-scale separation of relatively coarse particles in the range of 100  $\mu\text{m}$ . Centrifugal devices are useful for the separation of much smaller particles (5–10  $\mu\text{m}$ ).

Sedimentation balances are available which provide a means of directly weighing particles at selected time intervals as they fall in a liquid system. For continuous observations, automatic recording balances are also available.

Fig. 88-20 illustrates a commercially available instrument called a Micromerograph which utilizes the principle of sedimentation in an air column. This instrument and others related to it in principle offer more rapid determinations than those which utilize a liquid medium. There are, however, serious uncertainties in the method which must be taken into

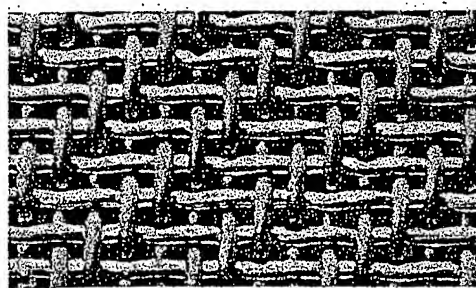


Fig. 88-19. Twilled weave screen.

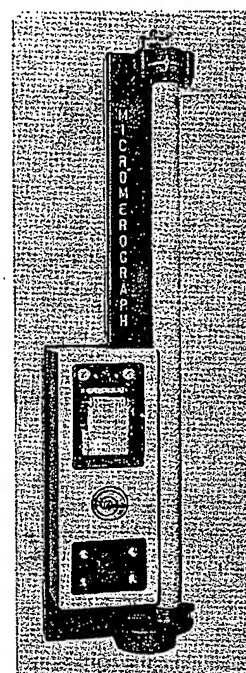


Fig. 88-20. Micromerograph (courtesy of the manufacturer).

consideration. Deviations from Stokes of particles against the inner wall of the sources of possible error.

The Carey and Stairmand photosedimentographs the tracks of particles as they fall in a fluid. The size determination is derived from the photographic track, which is an indication of the distance traveled by the particles, and the time of fall.

**Elutriation**—In this process the particles are suspended in a moving fluid, generally water or air. At any particular velocity of the fluid, particles will move upwards with the fluid, while particles that settle out under the influence of gravity will settle to the bottom of the chamber. Normal elutriation techniques, both undersize and oversize separation, each fraction and recycling is required if a stream of suspended particles is to be separated into fractions. By varying the fluid velocities stepwise the particles can be separated into fractions. The amount of material in each fraction can be determined and the size limits calculated from the Stokes' equation or measured directly by elutriation usually will give a sharper fractionation than will water elutriation.

Centrifugal elutriation is basically the same as elutriation, but in this case the fluid stream is caused to rotate by a high centrifugal force to the suspension of particles which are too large to follow the fluid stream and separate out on the walls or bottom of the chamber. The finer particles escape with the discharge stream. The separation down to about 0.5  $\mu\text{m}$  can be achieved with centrifugal classifiers.

The Dorr-Oliver (Dorr-Oliver) shown in Fig. 88-21 is an example of a centrifugal type classifier. The material is fed into the upper section. Centrifugal force throws the coarser particles to the outer wall and then drop down and out of the bottom of the classifier. The finer particles move to the inner spiral of the vortex and finally out of the top of the classifier.

The Sharples Super Classifier (Fig. 88-22) is an example of a centrifugal classifier useful for the separation of fine particles.

to provide a step towards the evaluation of the physiological availability of the drug substance, but as currently described it is not designed to measure the safety or effectiveness of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate *in vivo* studies and clinical evaluation. Like the disintegration test, it does provide a means of control in assuring that a given tablet formulation is the same as regards dissolution as the batch of tablets shown initially to be clinically effective. It also provides an *in vitro* control procedure to eliminate variations among production batches. The tablets for which a compendial dissolution requirement is provided include the following: Acetohexamide, Digitoxin, Digoxin, Hydrochlorothiazide, Meprobamate, Methandrostenolone, Methylprednisolone, Nitrofurantoin, Prednisolone, Prednisone, Quinidine Sulfate, Sulfamethoxazole, and the tablet containing the combination of theophylline, ephedrine hydrochloride, and phenobarbital.

Many procedures have been proposed for determining the dissolution rates of active substances from solid dosage forms. Three types of apparatus are officially recognized: Apparatus 1 (USP basket method), Apparatus 2 (USP paddle method), and Apparatus 3 (modified disintegration equipment method). The basket method is preferred by the USP unless otherwise indicated in the monograph. The suitability of a given apparatus for the dissolution test is determined by individually testing one tablet of the USP Dissolution Calibrator, Disintegrating Type (a prednisone tablet), and one tablet of the USP Dissolution Calibrator, Nondisintegrating Type (a salicylic acid tablet). The given type of apparatus is suitable if the results obtained with each tablet are within the stated acceptable range for that calibrator in the apparatus tested.

Apparatus 1 consists of a 40-mesh stainless steel basket placed on the end of the stirring shaft of a variable speed motor. The basket containing the tablet or capsule is immersed in the dissolution fluid designated and rotated at a speed indicated in the monograph. The dissolution fluid specified in the monograph could be one of the following: water, buffer solution, or dilute hydrochloric acid solution. The dissolution fluid is maintained at the temperature of 37°C and the volume of the fluid kept constant by adding a volume equal to that removed for sampling purposes. Samples of the fluid are removed at designated intervals and analyzed (see Fig. 89-6).

The apparatus for the paddle method includes a round bottom, 1000-ml container which can be placed in a constant temperature bath to hold the dissolution fluid at 37°C (see Fig. 89-6). The cover for the container has three ports providing openings for the stirring shaft, thermometer, and one for the removal of samples and replacement of dissolution fluid. The stirring shaft, attached to a varying speed motor, has a blade (paddle) held in a horizontal position near the bottom of the container. The tablet is dropped into the designated fluid through one of the ports and stirred at the rate indicated in the monograph. Samples are withdrawn and analyzed at indicated intervals. Both procedures allow for manual or automated timed-sample removal and testing. The automated procedure is helpful in controlling high-volume products.

Apparatus 3 consists of a modified USP disintegration apparatus. For the dissolution application no plastic disks are used; the bottom of the basket-rack assembly descends to 1 cm from the inside bottom surface of the vessel on the downward stroke; the 10-mesh stainless steel cloth in the basket-rack assembly is replaced with 40-mesh stainless steel cloth; and the 40-mesh stainless steel cloth is fitted to the top of the basket-rack assembly to prevent the solid dosage form from floating out of the assembly's plastic tubes.

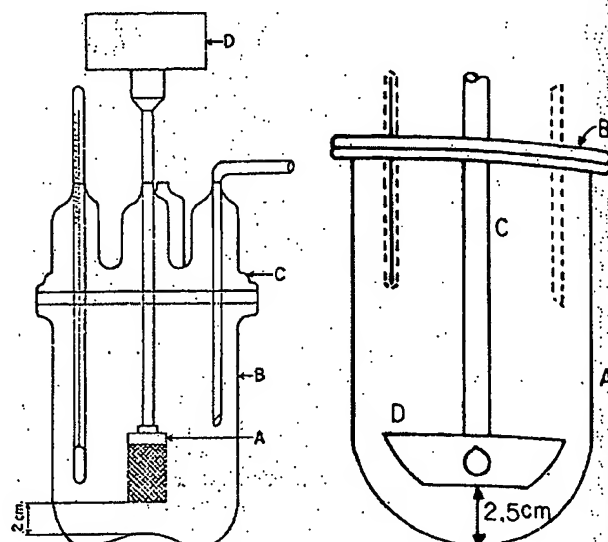


Fig. 89-6. Apparatus 1: A—rotating basket assembly; B—container for dissolution fluid; C—4-hole cover for container; D—varying speed stirring motor.

Apparatus 2: A—container for dissolution fluid; B—3-hole cover for container; C—stirring shaft attached to varying speed motor; D—stirring blade (paddle) held in horizontal position.

Details of the interpretation of dissolution test results are provided in the USP.

## Methods of Preparation

### Wet-Granulation Method

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on the large scale. The steps in the wet method are (1) weighing, (2) mixing, (3) granulation, (4) screening the damp mass, (5) drying, (6) dry screening, (7) lubrication, and (8) compression. The equipment involved

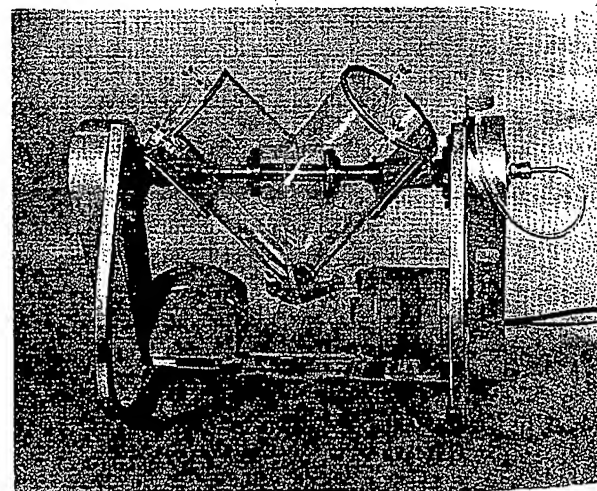


Fig. 89-7. Twin-shell blender for solids or liquid-solids blending (courtesy, Patterson-Kelley).



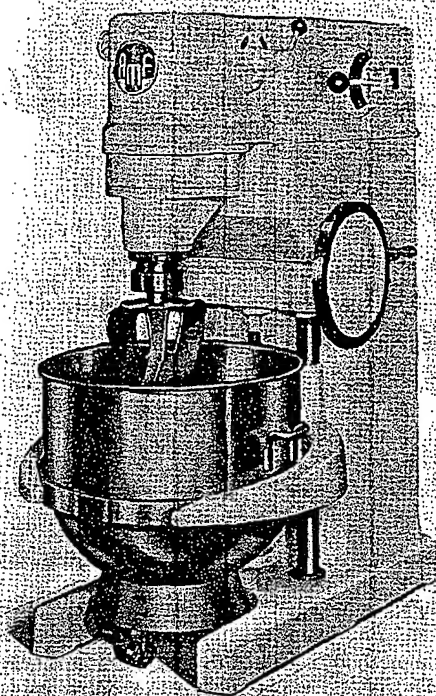


Fig. 89-8. The Glen powder mixer (courtesy, Am. Machine).

depends on the quantity or size of the batch. The active ingredient, diluent, and disintegrator are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars. Small-scale blending also can be carried out on a large piece of paper by holding opposite edges and tumbling the material back and forth. The powder blend may be sifted through a screen of suitable fineness to remove or break up lumps. This screening also affords additional mixing. The screen selected should always be of the same type of wire or cloth that will not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is deleteriously affected by even small amounts of copper, thus care must be taken to avoid contact with copper or copper-containing alloys.

For larger quantities of powder the Patterson-Kelley twin-shell blender and the double-cone blender offer means of precision blending and mixing in short periods of time (Fig. 89-7). Twin-shell blenders are available in many sizes from laboratory models to large production models. Blenders of the vertical shift type, e.g., the Glen mixer and the Hobart mixer, have served this function in the pharmaceutical industry for many years (Fig. 89-8). On a large scale, ribbon blenders are also frequently employed and may be adapted for continuous production procedures.

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is overwetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression. For larger quantities mass mixers of the sigma-blade type have been widely used in the pharmaceutical industry (Fig. 89-9). Twin-shell blenders are also constructed to permit the binding solution to be sprayed on the powder blend for granulation following the mixing operation.

The wet granulation is forced through a 6- or 8-mesh screen.

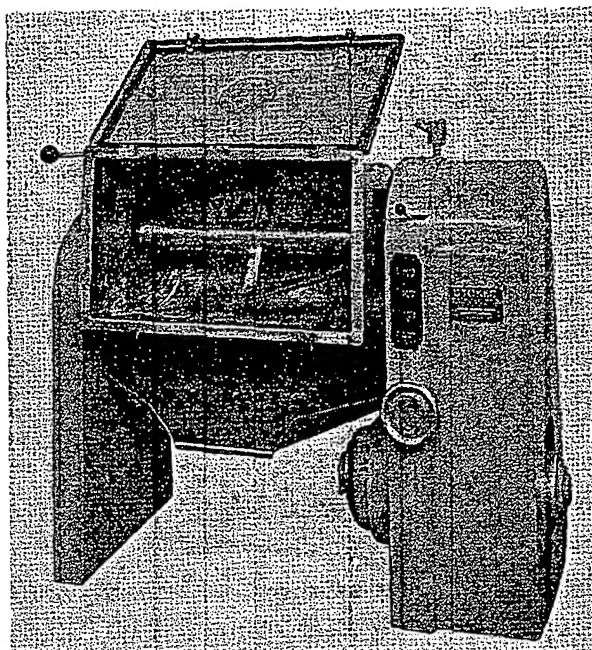


Fig. 89-9. Mass mixer for granulations (courtesy, Stokes).

Small batches can be forced through by hand using a manual screen. For larger quantities one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, the Colton rotary granulator, the Fitzpatrick comminuting mill, or the Stokes tornado mill. See Fig. 89-10. In addition to the comminuting mills in which the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars, a Swiss milling machine called the Artotex (*Excelsior*) cylindrical shredder is being used. The milling chamber consists of a rotating shredding drum into

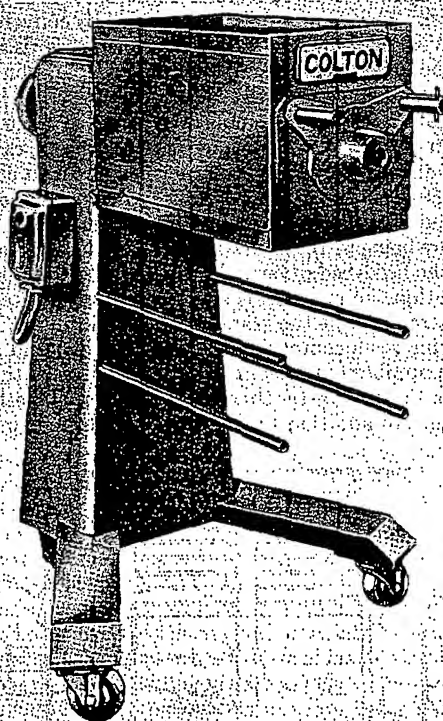


Fig. 89-10. Rotary granulator and sifter (courtesy, Vector/Colton).

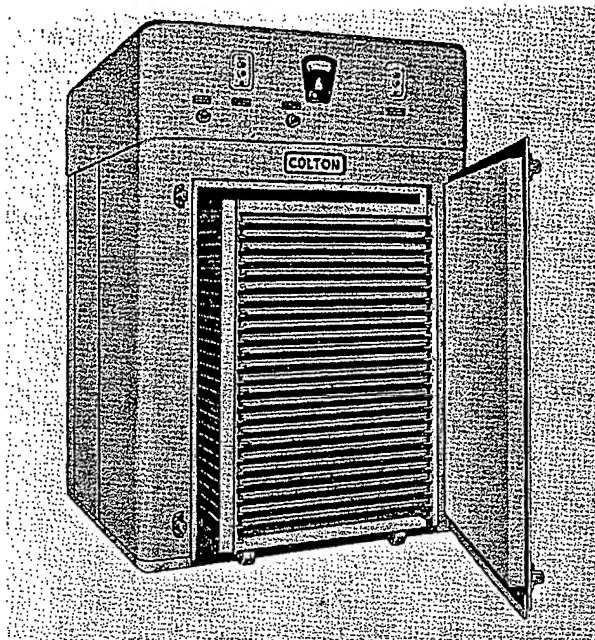


Fig. 89-11. Tray dryer oven (courtesy, Vector/Colton).

which the material flows and is sheared against the sides of the drum by impeller blades rotating at a higher speed. This action plus centrifugal force results in the formation of distinct granules. Although it can be used for either wet or dry granulations, the significant advantage claimed is its ability to granulate efficiently extremely wet masses.

For tablet formulations where continuous production is justified, extruders such as the Reitz extruder have been adapted for the wet-granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent and the wet mass is gradually forced through a perforated screen forming threads of the wet granulation. The granulation is then dried by conventional methods. A semiautomatic continuous process using the Reitz extruder has been described for the preparation of the antacid tablet Gelusil (Warner-Lambert).

Moist material from the granulator is placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Figs. 89-11 and 89-12. While tray drying is the most widely used method of drying tablet granulations, other methods are being introduced with success. Notable among these are the fluid-bed dryers. In drying tablet granulations by fluidization the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time the

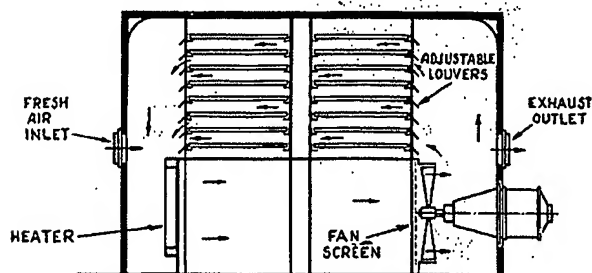


Fig. 89-12. Cross section of tray dryer.

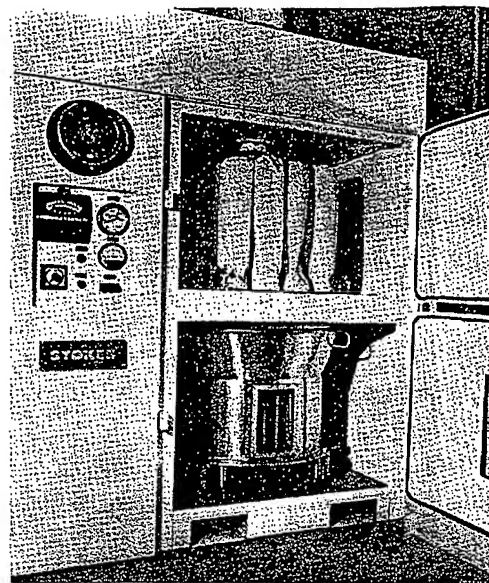


Fig. 89-13. Fluid bed dryer (courtesy, Stokes).

fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Fig. 89-13.

The application of radio-frequency drying and infrared drying to tablet granulations has been reported as successful for the majority of granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovac dryer system by Ciba pharmacists and engineers. The dryer is similar in appearance to the cone blender except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved because of the moving bed, the controlled temperature, and the controlled time period of the drying cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature as well as by comminuting the granulation to the desired granule size after drying.

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients such as gums in a hydrated state. Also the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process an effort is made to obtain a uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

After drying, the granulation is reduced in particle size by passing it through a smaller mesh screen. Following dry screening the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested.

Tablets up to  $\frac{1}{16}$ -in. diam, use 20-mesh  
 Tablets  $\frac{1}{32}$  in. to  $\frac{1}{16}$  in., use 18-mesh  
 Tablets  $\frac{1}{32}$  in. to  $\frac{1}{16}$  in., use 14-mesh  
 Tablets  $\frac{1}{16}$  in. and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a wooden block. With larger quantities, any of the comminuting mills with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose, and magnesium trisilicate, a relationship has been demonstrated to exist between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle-size distribution did not appear to influence hardness or disintegration.

After dry granulation, the lubricant is added as a fine powder. It is usually screened onto the granulation through 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the dry-granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as "fines," also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Air trapped in the tablets by the fine powder causes them to split apart after ejection from the machine. Fines, however, at a level of 10–20% are traditionally sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Recently, even higher concentrations of fines were successfully used in tablet manufacture. Some investigators maintain that no general limits exist for the amount of fines that can be present in a granulation but must be determined for each specific formula.

Another approach toward the faster preparation of tablet granulations has come from the utilization of the air-suspension technique developed by Wurster.<sup>11</sup> In this method particles of an inert material, or the active drug, are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation which is ready for compression after addition of the lubricant. In addition to its use for the preparation of tablet granulations this technique also has been proposed for the coating of solid particles as a means of improving the flow properties of small particles (see page 1587). Methods for the preparation of compressed tablets have been reviewed in the literature.<sup>12</sup>

In the Merck Sharp & Dohme facility at Elkton, Virginia, the entire tablet manufacturing process based on a wet-granulation method is computer-controlled. By means of a computer, the system weighs the ingredients, blends, granulates, dries, and lubricates to prepare a uniform granulation of specified particle size and particle size distribution. The computer directs the compression of the material into tablets having exacting specifications for thickness, weight, and hardness. After compression, the tablets are coated with a

water-based film coating. The computer controls and monitors all flow of material. The facility represents an innovation in pharmaceutical manufacturing. See Fig. 89-14.

#### Dry-Granulation Method

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or the double-compression method. It eliminates a number of steps but still includes (1) weighing, (2) mixing, (3) slugging, (4) dry screening, (5) lubrication, and (6) compression. The active ingredient, diluent (if one is required), and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. Also, producing large slugs decreases production time;  $\frac{1}{8}$  to 1 in. are the most practical sizes for slugs. Sometimes, to obtain the pressure which is desired the slug sizes are reduced to  $\frac{3}{4}$  in. The punches should be flat-faced. The compressed slugs are comminuted through the desirable mesh screen either by hand, or for larger quantities through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation, blended gently, and the material is compressed into tablets. Aspirin is a good example where slugging is satisfactory. Other materials such as aspirin combinations, acetophenetidin, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds may be treated similarly.

Results comparable to those accomplished by the slugging process are also obtained with compacting mills. In the compaction method the powder to be densified passes between high-pressure rollers which compress the powder and remove the air. The densified material is reduced to a uniform granule size and compressed into tablets after the addition of a lubricant. Excessive pressures which may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator (Fitzpatrick) and the Compactor Mill (Allis-Chalmers).

#### Direct Compression

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, permanganate), ammonium chloride, and methenamine. These materials possess cohesive and flow properties which make direct compression possible.

Since the pharmaceutical industry is constantly making efforts to increase the efficiency of tableting operations and to reduce costs by utilizing the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation. Also, this method should produce tablets of faster dissolution rates because no colloidal binders such as gelatin or starch are used to surround the granules. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the



which have not been compressed, thus keeping the circular pressing compartment and the upper and lower punch guides free of dust.

Drug manufacturers have the responsibility to make certain that microorganisms present in finished products are unlikely to cause harm to the patient and will not be deleterious to the product. An outbreak of *Salmonella* infections in Scandinavian countries was traced to thyroid tablets which had been prepared from contaminated thyroid powder. This concern eventually led to the establishment of microbial limits for raw materials of animal or botanical origin, especially those that

readily support microbial growth and are not rendered sterile during subsequent processing. Harmful microorganisms when present in oral products include *Salmonella* sp., *E. coli*, certain *Pseudomonas* sp. such as *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The compendia have microbial limits on raw materials such as aluminum hydroxide gel, corn starch, thyroid, acacia, and gelatin.

These represent examples of the industry's efforts to conform with the intent of current good manufacturing practice as defined by the Food and Drug Administration (see page 1436).

### Tablet Formulations

#### Wet Granulation Method

##### CT Acetaminophen, 300 mg

Ingredients	In each	In 10,000
Acetaminophen	3000 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose	61.75 mg	617.5 g
Alcohol 3A—200 proof	4.5 ml	45 l
Stearic acid	9 mg	90 g
Talc	13.5 mg	135 g
Corn starch	43.25 mg	432.5 g

Blend acetaminophen, polyvinylpyrrolidone, and lactose together; pass through a 40-mesh screen. Add the alcohol slowly and knead well. Screen the wet mass through a 4-mesh screen. Dry granulation at 50°C overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid, talc, and corn starch through 60-mesh screen prior to mixing by tumbling with the granulation. Compress using  $\frac{7}{16}$ -in. standard concave punch. 10 tablets should weigh 4.5 g (courtesy, Abbott).

##### CT Ascorbic Acid USP, 50 mg

Ingredients	In each	In 7000
Ascorbic Acid USP (powder No. 80) <sup>a</sup>	55 mg	385 g
Lactose	21 mg	147 g
Starch (potato)	13 mg	91 g
Ethylcellulose N 100 (80–105 cps)	16 mg	112 g
Starch (potato)	7 mg	49 g
Talc	6.5 mg	45.5 g
Calcium stearate (impalpable powder)	1 mg	7 g
Weight of granulation		836.5 g

<sup>a</sup> Includes 10% in excess of claim.

Granulate the above first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol adding additional anhydrous alcohol to obtain good wet granules. Wet screen through 8 stainless steel screen and dry at room temperature in an air-conditioned area. Dry screen through 20 stainless steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat beveled,  $\frac{1}{4}$ -in. punch. 20 tablets should weigh 2.39 g.

#### Chewable Antacid Tablets

Ingredients	In each	In 10,000
Magnesium trisilicate	500 mg	5000 g
Aluminum hydroxide, dried gel	250 mg	2500 g
Mannitol	300 mg	3000 g
Sodium saccharin	2 mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Corn starch	10 mg	100 g

Mix the magnesium trisilicate and aluminum hydroxide with the mannitol. Dissolve the sodium saccharin in a small quantity of purified water, then combine this with the starch paste. Granulate the powder blend with the starch paste. Dry at 140°F and screen through 16-mesh screen. Add the flavoring oil, magnesium stearate, and corn starch; mix well. Age the granulation for at least 24 hours and compress using  $\frac{5}{16}$ -in. flat-face bevel-edge punch (courtesy, Atlas).

#### CT Hexavitamin

Ingredients	In each	In 7000
Ascorbic Acid USP (powder) <sup>a</sup>	82.5 mg	577.5 g
Thiamine Mononitrate USP (powder) <sup>a</sup>	2.4 mg	16.8 g
Riboflavin <sup>a</sup>	3.3 mg	23.1 g
Nicotinamide USP (powder) <sup>a</sup>	22 mg	154 g
Starch	...	97.4 g
Lactose	...	41.2 g
Zein	...	45 g
Vitamin A acetate:	6250 U	
Vitamin D <sub>2</sub> <sup>a</sup> (use Pfizer crystals medium granules containing 500,000 U vitamin A acetate and 50,000 U vitamin D <sub>2</sub> /g).	625 U	87.5 g
Magnesium stearate		7.5 g
Weight of granulation		1050 g

<sup>a</sup> Includes following excess of claim: ascorbic acid 10%, thiamine mononitrate 20%, riboflavin 10%, nicotinamide 10%, and vitamin A acetate-vitamin D<sub>2</sub> crystals 25%.

Thoroughly mix the first six ingredients and granulate with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good wet granules). Wet screen through 8 stainless steel screen and dry at 110–120°F. Dry screen through 20 stainless steel screen and add the vitamin crystals. Mix thoroughly, lubricate and compress. 10 tablets should weigh 1.50 g. Coat with syrup.

**CT Theobromine-Phenobarbital**

Ingredients	In each	In 7000
Theobromine	325 mg	2275 g
Phenobarbital	33 mg	231 g
Starch	39 mg	273 g
Talc	8 mg	56 g
Acacia (powder)	8 mg	56 g
Stearic acid	0.7 mg	4.9 g
Weight of granulation		2895.9 g

Prepare a paste with the acacia and an equal weight of starch. Use this paste for granulating the theobromine and phenobarbital. Dry and put through a 12-mesh screen, add the remainder of the material, mix thoroughly, and compress into tablets, using a  $\frac{1}{32}$ -in. concave punch. 10 tablets should weigh 4.13 g.

**Dry Granulation Method****CT Acetylsalicylic Acid**

Ingredients	In each	In 7000
Acetylsalicylic Acid (crystals 20-mesh)	0.325 g	2275 g
Starch		226.8 g
Weight of granulation		2501.8 g

Dry the starch to a moisture content of 10%. Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14–16 mesh size. Recompress into tablets, using a  $\frac{1}{32}$ -in. punch. 10 tablets should weigh 3.575 g.

**CT Sodium Phenobarbital**

Ingredients	In each	In 7000
Phenobarbital sodium	65 mg	455 g
Milk sugar (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14–16-mesh granules. Recompress into tablets, using a  $\frac{1}{32}$ -in. concave punch. 10 tablets should weigh 1.3 g.

**CT Vitamin B Complex**

Ingredients	In each	In 10,000
Thiamine mononitrate <sup>a</sup>	0.733 mg	7.33 g
Riboflavin <sup>a</sup>	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate <sup>a</sup>	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Milk sugar (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1250 g

<sup>a</sup> Includes 10% in excess of claim.

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14–16-mesh granules. Recompress into tablets, using a  $\frac{1}{4}$ -inch concave punch. 10 tablets should weigh 1.25 g.

Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

**Direct Compression Method****APC Tablets**

Ingredients	In each	In 10,000
Aspirin (40-mesh crystal)	224 mg	2240 g
Phenacetin	160 mg	1600 g
Caffeine (Anhyd. USP gran.)	32 mg	320 g
Compressible sugar (Di-Pac <sup>a</sup> )	93.4 mg	934 g
Sterotex	7.8 mg	78 g
Silica gel (Syloid 244 <sup>b</sup> )	2.8 mg	28 g

<sup>a</sup> Amstar.

<sup>b</sup> Davison Chem.

Blend ingredients in twin-shell blender for 15 minutes and compress on  $\frac{1}{32}$ -in. standard concave punch (courtesy, Amstar).

**CT Ascorbic Acid USP, 250 mg**

Ingredients	In each	In 10,000
Ascorbic Acid USP (Merck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose <sup>a</sup>	159 gm	1590 g
Stearic acid	9 mg	90 g
Colloidal silica <sup>b</sup>	2 mg	20 g
Weight of granulation		4250 g

<sup>a</sup> Avicel-PH-101.

<sup>b</sup> Cab-O-Sil.

Blend all ingredients in a suitable blender. Compress using  $\frac{7}{16}$ -in. standard concave punch. 10 tablets should weigh 4.25 g (courtesy, FMC).

**Breath Freshener Tablets**

Ingredients	In each	In 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244 <sup>a</sup> )	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

<sup>a</sup> Davison Chem.

Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on  $\frac{5}{16}$ -in. flat-face bevel-edge punch to a thickness of 3.1 mm (courtesy, Atlas).

**Chewable Antacid Tablets**

Ingredients	In each	In 10,000
Aluminum hydroxide and Magnesium carbonate, co-dried gel <sup>a</sup>	325 mg	3250 g
Mannitol USP (granular)	675 mg	6750 g
Microcrystalline cellulose <sup>b</sup>	75 mg	750 g
Corn starch	30 mg	300 g
Calcium stearate	22 mg	220 g
Flavor	qs	qs

<sup>a</sup> Reheis F-MA-11.

<sup>b</sup> Avicel.

Blend all ingredients in a suitable blender. Compress using  $\frac{5}{16}$ -in. flat-face bevel-edge punch (courtesy, Atlas).



21<sup>ST</sup> EDITION

# *Remington*

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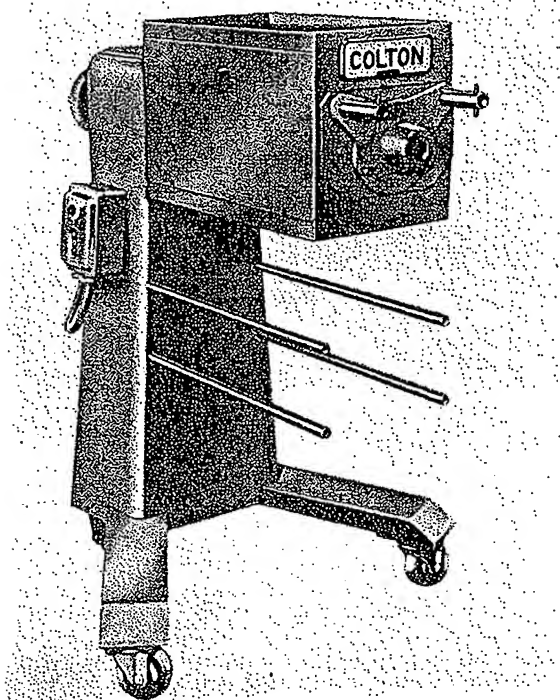


Figure 45-10. Rotary granulator and sifter (courtesy, Vector/Colton).

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6- or 8-mesh screen. Small batches can be forced through by hand using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill, or Stokes tornado mill. See Figure 45-10. In comminuting mills the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars. Most high-speed mixers are equipped with a chopper blade that operates independently of the main mixing blades and can replace the wet milling step, i.e., can obviate the need for a separate operation.

For tablet formulations in which continuous production is justified, extruders such as the Reitz extruder have been adapted for the wet-granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent, and the wet mass gradually is forced through a perforated screen, forming threads of the wet granulation. The granulation then is dried by conventional methods. A semiautomatic, continuous process using the Reitz extruder has been described for the preparation of the antacid tablet Gelusil (Warner-Lambert/Pfizer).

Moist material from the wet milling step traditionally was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Figure 45-11. While tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now considered the standard. In drying tablet granulation by fluidization, the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed

and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Figure 45-12.<sup>31</sup>

The application of microwave drying and infrared drying to tablet granulations has been reported as successful for moist granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovne dryer system by Ciba/Novartis pharmacists and engineers. The dryer is similar in appearance to the cone blender except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved because of the moving bed, controlled temperature, and controlled time period of the drying cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature as well as by comminuting the granulation to the desired granule size after drying.

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in a hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, an effort is made to obtain a uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present in granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

After drying, the granulation is reduced in particle size by passing it through a smaller-mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested:

Tablets up to  $\frac{1}{8}$  inch diameter, use 20-mesh  
Tablets  $\frac{1}{8}$  to  $\frac{1}{4}$  inch, use 16-mesh  
Tablets  $\frac{1}{4}$  to  $\frac{1}{2}$  inch, use 14-mesh  
Tablets  $\frac{1}{2}$  inch and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless steel spatula. With larger quantities, any of the comminuting mills

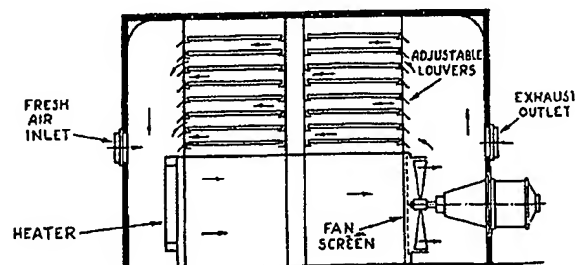


Figure 45-11. Cross-section of tray dryer.



# PHARMACEUTICAL DOSAGE FORMS

Tablets

*SECOND EDITION, REVISED AND EXPANDED*

---

In Three Volumes

VOLUME 1

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heating and cooling, a vacuum take-off, and a liquid dispersion bar through which a liquid binder can be added. As the blender rotates, liquid is sprayed into the powder charge through the rotating liquid dispersion bar, located concentric to the trunnion axis. The bar's dog-eared blades, rotating at 3300 rpm, aerates the powder to increase the speed and thoroughness of the blend. Granulation can be controlled by the rate of binder addition through the dispersion bar. After heating, the liquid of the binder is removed under reduced pressure. Mixing, granulating, heating, cooling, and removal of excess liquid are carried out in a continuous operation in an enclosed system, thereby protecting the contents from contamination and the adjacent area from contamination by the contents. Once the granulation process is completed, the remaining excipients can be added and blended by the simple rotating action of the blender. This unit is also known as a liquid-solids processor.

#### IV. GRANULATION

Most powders cannot be compressed directly into tablets because (a) they lack the proper characteristics of binding or bonding together into a compact entity and (b) they do not ordinarily possess the lubricating and disintegrating properties required for tableting. For these reasons, drugs must first be pretreated, either alone or in combination with a filler, to form granules that lend themselves to tableting. This process is known as granulation.

Granulation is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates [22] to render them into a free-flowing state similar to that of dry sand.

Size enlargement, also called agglomeration, is accomplished by some method of agitation in mixing equipment or by compaction, extrusions or globulation as described in the previous section on unit operations [4,23, 24].

The reasons for granulation as listed by Record [23] are to:

1. Render the material free flowing
2. Densify materials
3. Prepare uniform mixtures that do not separate
4. Improve the compression characteristics of the drug
5. Control the rate of drug release
6. Facilitate metering or volume dispensing
7. Reduce dust
8. Improve the appearance of the tablet

Because of the many possible approaches to granulation, selection of a method is of prime importance to the formulator.

##### A. Wet Granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. This process has been extensively reviewed by Record [23], Kristensen and Schaefer [26], and Capes [27].



**For The United States Patent and Trademark Office**

Applicants: P. Bertelsen et al.  
Application no.: 09/786,864  
National Filing Date: 10 July 2001  
For: Quick release pharmaceutical compositions of drug substances  
Examiner: Pulliam, Amy E  
Art unit: 1615

**DECLARATION OF POUL BERTELSEN**

1. I, **Poul Bertelsen**, of Copenhagen, Denmark, one of the named inventors of the above-captioned patent application do state and declare as follows:
2. I believe that I am a person skilled in the art to which the above-captioned application pertains. I am a Senior Research Scientist within the field of Pharmaceutical Development and have 15 years working experience with the formulation of pharmaceuticals.
3. I have read and understood the pending claims in the application in question, the first Office Action related thereto, dated 23 September 2002, and the cited prior art (Masami et al). In respect to the first Office Action, I have the following comments:
4. It is my understanding that Masami et al describes a method for improving the dissolution of NSAIDs in gastric fluid by including an alkaline substance in the composition.
5. I wish to remark that it is my further understanding that such alkaline-containing compositions of Masami et al are manufactured by a process including a conventional granulation step (see embodiments 1-8 of Masami et al).
6. According to pharmaceutical textbooks, the term "granulation" relates to a process for treating powders so as to make the powder more suitable for being compressed into tablets. During the granulation process, smaller particles are gathered together into larger, permanent "aggregates" that may be termed granules. See enclosed copy of reference, pharmaceutical Dosage Forms: Tablets volume 1, Marcel Dekker, Inc., Edited by Herbert A. Lieberman, Leon Lachman and Joseph B. Schwartz, 1989, page 148.
7. According to Masami et al, the particle size of the granules may pass a sieve of 20 Mesh or less (see page 5, last sentences of the translated application). I wish to remark that particles that passes a sieve of 20 Mesh relates to



particles with a particle size of less than about 800  $\mu\text{m}$ . Thus, compositions of Masami et al is based on particulate compositions with a particle size of less than 800  $\mu\text{m}$ .

8. However, the present application is not directed to compositions manufactured by conventional granulation processes. The present application describes compositions processed under conditions wherein the drug and the alkaline substance is being contacted with an aqueous medium. This step is included in conventional granulation processes. However, according to the present invention, the mean particle size of the initial mixtures of the drug and alkaline substance should only increase within a narrow range upon being exposed to aqueous medium and dried. The increase in the mean particle size should be less than 100% in relation to the starting point. Furthermore, the overall particle size of the particulate composition before being exposed to aqueous solution and dried should be rather small in that the powder before being contacted with water should be such that at least 90% w/w of the particles passes through sieve 180  $\mu\text{m}$ . After being contacted with an aqueous medium to form a particulate composition the particle size should be such that at least 50% w/w of the particles passes through sieve 180  $\mu\text{m}$ .
9. I firmly believe that Masami et al failed to recognise some problems with the compositions processed by conventional granulation in that the process of enlarging the particle sizes by granulation (formation of aggregates) leads to poorer dissolution rates.
10. Under my supervision experiments have been carried out, which demonstrate that upon manufacturing a composition based on a particulate composition with enlarged particle sizes such as Masami et al., the release of NSAID from such a composition is not fast, but about 38% within 20 minutes of dissolution testing in 0.07 M hydrochloric acid. See data enclosed in Appendix A. I wish to note that the particulate composition in this example was fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm, upon where particles in the size range of 500 to 800  $\mu\text{m}$  is selected. This size range is in agreement with the upper limit defined in Masami et al.
11. It is my conclusion that compositions of Masami et al, which are based on particulate compositions with particle size of 800  $\mu\text{m}$  or less, is not likely to result in quick release of the drug substance such that at least 50% of the drug substance is dissolved within 20 minutes of dissolution testing.
12. According to the present invention the step of contacting an alkaline substance with the active ingredient in an aqueous medium is also an essential element of the invention. However, on the basis of my experimental work, I am convinced that the step of including an alkaline substance in contact with the active ingredient may not inherently result in

the quick release of an NSAID upon dissolving the composition in gastric fluid. According to my understanding, the quick release is not just a matter of including an alkaline substance in the composition. The particle size of the particulate composition, wherein the active ingredient and the alkaline substance is in contact with each other, is an essential feature. Therefore, in order to ensure quick release (50% dissolved within 20 minutes of dissolution testing in gastric fluid) the particle size of the particulate composition that has been contacted with water should be such that at least 50% of the particles has a particle size of less than 180  $\mu\text{m}$ .

13. As can be seen from examples 6 and 9 in the present application, the release rate from the composition depends on the particle size of the final particulate composition comprising the active ingredient and the alkaline substance after being contacted with aqueous solution and dried. Example 6 demonstrates the effect of increasing the particle size of the particulate composition. Even a slightly change in the mean particle size below or above 212  $\mu\text{m}$  markedly affects the dissolution rate. For example, a tablet composition based on a particulate composition with a mean particle size less than 212  $\mu\text{m}$  results in 93.1% dissolved NSAID after 20 minutes dissolution testing. Conversely, a tablet based on particulate composition with a mean particle size above 212  $\mu\text{m}$  results in 85.4% dissolved NSAID after 20 minutes dissolution testing. Thus, upon decreasing the mean particle size of the particulate composition the dissolution rate becomes markedly faster. From example 9 it can be seen that in the case wherein about 60% of the particulate composition has a particle size less than 180  $\mu\text{m}$ , the amount of dissolved NSAID within the first 20 minutes of dissolution testing is no more than 65.8 %.
14. I wish to note that the particle sizes of the particulate composition in examples 6 and 9 are well below the particle sizes of the particulate compositions of Masami et al. As stated, the compositions based on a particulate composition with higher particle sizes such that up to 800  $\mu\text{m}$  will not lead to fast dissolution of the NSAID drugs.
15. I solved the problem seen with compositions of Masami et al by selecting significant lower particle sizes of that particulate composition, which subsequently may be compressed into tablets or filled into capsules or the like.
16. In light of the above-mentioned items 1 to 14, I firmly believe that the present invention contributes considerable to the art in that it is not obvious to the skilled person that smaller particle sizes may result in improved release rate, while still achieving oral dosage form with good mechanical resistance.

19 dec. 2002  
Date:

Poul Bertelsen  
Poul Bertelsen

## Appendix A

### Preparation of particulate composition with particle size of about 500 to 800 nm

Batch No. 19029835 was prepared.

Lornoxicam particulate composition was prepared using the following ingredients.

	Ingredients:	Amount (g)
I	Lornoxicam	7.5
II	Sodium bicarbonate	37.7
III	Cellulose, microcrystalline	90.4
IV	Dibasic Calcium Phosphate, Anhydrous	104.1
V	Low-substituted Hydroxypropyl Cellulose	45.3
VI	Hydroxypropylcellulose	15
VII	Purified water	115.8
VIII	Ethanol 99.9 %	38.7

The ingredients II to IV were mixed in a Moulinex laboratory size mixer and mixed for 5 min. To 100 g of this mixture Ingredient I was added and mixed in a cubus mixer for 5 min. The resulting mass was screened through a 0.5 mm screen and returned to the Moulinex mixer and mixed for further 6 min. A premixed mixture of Ingredient VII and VIII was added to the powder mixture and massed for 6 min.

The resulting mass was extruded in a Nica E 140 extruder with a screen size of 0.6 mm. The extrudate was spheronized in a laboratory size spheronizer at a rotation speed of 700 rpm for 4 min. The particulate composition thus produced were dried in a laboratory size fluid bed dryer with an inlet temperature of approximately 400 °C, and the drying process was continued until the outlet temperature has reached approximately 300 °C. The total drying time was approximately 25 min.

The dried particulate composition was fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm, thereby selecting particles in the range of 500 to 800 nm.

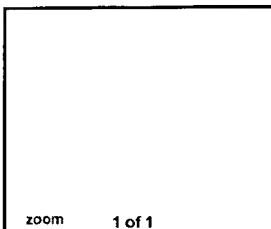
The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
After 1h	37.8

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zoom 1 of 1

**Synonym**Cellulose microcrystalline  
Cellulose powder  
Cellulose  
Cellulosum microcristallinum  
Cotton linters**CAS Number**

9004-34-6

**MDL number**

MFCD00081512

**EG/EC Number**

232-674-9

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